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CHEMICAL COMPOUNDS

The present invention relates to heterocyclic derivatives having pharmaceutical activity, to processes for preparing such derivatives, to pharmaceutical compositions comprising such derivatives and to the use of such derivatives as active therapeutic agents.

Pharmaceutically active piperidine derivatives are disclosed in WO01/87839, EP-A1-1013276, WO00/08013, WO99/38514, WO99/04794, WO00/76511, WO00/76512, WO00/76513 and WO00/76514.

Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation and also play a rôle in the maturation of cells of the immune system. Chemokines play an important rôle in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C, or α) and Cys-Cys (C-C, or β) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1 α and 1 β (MIP-1 α and MIP-1 β).

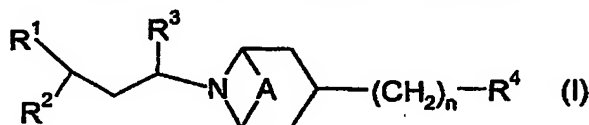
Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

The CCR5 receptor is expressed on T-lymphocytes, monocytes, macrophages, dendritic cells, microglia and other cell types. These detect and respond to several chemokines, principally "regulated on activation normal T-cell expressed and secreted" (RANTES), macrophage inflammatory proteins (MIP) MIP-1 α and MIP-1 β and monocyte chemoattractant protein-2 (MCP-2).

This results in the recruitment of cells of the immune system to sites of disease. In many diseases it is the cells expressing CCR5 which contribute, directly or indirectly, to tissue damage. Consequently, inhibiting the recruitment of these cells is beneficial in a wide range of diseases.

CCR5 is also a co-receptor for HIV-1 and other viruses, allowing these viruses to enter cells. Blocking the receptor with a CCR5 antagonist or inducing receptor internalisation with a CCR5 agonist protects cells from viral infection.

The present invention provides a compound of formula (I):



wherein

A is absent or is (CH₂)₂;

R¹ is C₁₋₈ alkyl, C(O)NR¹⁰R¹¹, C(O)₂R¹², NR¹³C(O)R¹⁴, NR¹⁵C(O)NR¹⁶R¹⁷, NR¹⁸C(O)₂R¹⁹ heterocyclyl (for example piperidine, piperazine, pyrrolidine or azetidine), aryl or heteroaryl; R¹⁰, R¹³, R¹⁵, R¹⁶ and R¹⁸ are hydrogen or C₁₋₆ alkyl;

R¹¹, R¹², R¹⁴, R¹⁷ and R¹⁹ are C₁₋₈ alkyl (optionally substituted by halo, hydroxy, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl (optionally substituted by halo), C₅₋₆ cycloalkenyl, S(C₁₋₄ alkyl), S(O)(C₁₋₄ alkyl), S(O)₂(C₁₋₄ alkyl), heteroaryl, aryl, heteroaryloxy or aryloxy), aryl, heteroaryl, C₃₋₇ cycloalkyl (optionally substituted by halo or C₁₋₄ alkyl), C₄₋₇ cycloalkyl fused to a phenyl ring, C₅₋₇ cycloalkenyl, or, heterocyclyl (itself optionally substituted by oxo, C(O)(C₁₋₆ alkyl), S(O)_k(C₁₋₆ alkyl), halo or C₁₋₄ alkyl); or R¹¹, R¹², R¹⁴ and R¹⁷ can also be hydrogen;

or R¹⁰ and R¹¹, and/or R¹⁶ and R¹⁷ may join to form a 4-, 5- or 6-membered ring which optionally includes a nitrogen, oxygen or sulphur atom, said ring being optionally substituted by C₁₋₆ alkyl, S(O)_i(C₁₋₆ alkyl) or C(O)(C₁₋₆ alkyl);

R² C₁₋₆ alkyl, phenyl, heteroaryl or C₃₋₇ cycloalkyl;

R^3 H or C_{1-4} alkyl;

R^4 is aryl or heteroaryl;

n is 2, 3 or 4;

unless specified otherwise aryl, phenyl and heteroaryl moieties are independently optionally

- 5 substituted by one or more of halo, cyano, nitro, hydroxy, $OC(O)NR^{20}R^{21}$, $NR^{22}R^{23}$,
 $NR^{24}C(O)R^{25}$, $NR^{26}C(O)NR^{27}R^{28}$, $S(O)_2NR^{29}R^{30}$, $NR^{31}S(O)_2R^{32}$, $C(O)NR^{33}R^{34}$, CO_2R^{36} ,
 $NR^{37}CO_2R^{38}$, $S(O)_qR^{39}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{1-6} haloalkyl,
 C_{1-6} alkoxy(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, phenyl, phenyl(C_{1-4})alkyl, phenoxy,
phenylthio, phenylS(O), phenylS(O)₂, phenyl(C_{1-4})alkoxy, heteroaryl, heteroaryl(C_{1-4})alkyl,
10 heteroaryloxy or heteroaryl(C_{1-4})alkoxy; wherein any of the immediately foregoing phenyl and
heteroaryl moieties are optionally substituted with halo, hydroxy, nitro, S(C_{1-4} alkyl), S(O)(C_{1-4}
alkyl), S(O)₂(C_{1-4} alkyl), S(O)₂NH₂, S(O)₂NH(C_{1-4} alkyl), S(O)₂N(C_{1-4} alkyl)₂, cyano, C_{1-4}
alkyl, C_{1-4} alkoxy, C(O)NH₂, C(O)NH(C_{1-4} alkyl), C(O)N(C_{1-4} alkyl)₂, CO₂H, CO₂(C_{1-4} alkyl),
NHC(O)(C_{1-4} alkyl), NHS(O)₂(C_{1-4} alkyl), CF₃ or OCF₃;

- 15 unless otherwise stated heterocyclyl is optionally substituted by C_{1-6} alkyl [optionally
substituted by phenyl {which itself optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy,
cyano, nitro, CF₃, OCF₃, (C_{1-4} alkyl)C(O)NH, S(O)₂NH₂, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or
S(O)₂(C_{1-4} alkyl)} or heteroaryl {which itself optionally substituted by halo, C_{1-4} alkyl, C_{1-4}
alkoxy, cyano, nitro, CF₃, (C_{1-4} alkyl)C(O)NH, S(O)₂NH₂, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or
20 S(O)₂(C_{1-4} alkyl)}], phenyl {optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano,
nitro, CF₃, OCF₃, (C_{1-4} alkyl)C(O)NH, S(O)₂NH₂, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or S(O)₂(C_{1-4}
alkyl)}, heteroaryl {optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, CF₃,
(C_{1-4} alkyl)C(O)NH, S(O)₂NH₂, C_{1-4} alkylthio, S(O)(C_{1-4} alkyl) or S(O)₂(C_{1-4} alkyl)},
S(O)₂NR⁴⁰R⁴¹, C(O)R⁴², C(O)₂(C_{1-6} alkyl) (such as tert-butoxycarbonyl), C(O)₂(phenyl(C_{1-2}
25 alkyl)) (such as benzyloxycarbonyl), C(O)NHR⁴³, S(O)₂R⁴⁴, NHS(O)₂NHR⁴⁵, NHC(O)R⁴⁶,
NHC(O)NHR⁴⁷ or NHS(O)₂R⁴⁸, provided none of these last four substituents is linked to a
ring nitrogen;

k, l, p and q are, independently, 0, 1 or 2;

- R^{20} , R^{22} , R^{24} , R^{26} , R^{27} , R^{29} , R^{31} , R^{33} , R^{37} and R^{40} are, independently, hydrogen or C_{1-6} alkyl;
30 R^{21} , R^{23} , R^{25} , R^{28} , R^{30} , R^{32} , R^{34} , R^{36} , R^{38} , R^{39} , R^{41} , R^{42} , R^{43} , R^{44} , R^{45} , R^{46} , R^{47} and R^{48} are,
independently, C_{1-6} alkyl (optionally substituted by halo, hydroxy, C_{1-6} alkoxy, C_{1-6}
haloalkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, S(C_{1-4} alkyl), S(O)(C_{1-4} alkyl), S(O)₂(C_{1-4}
alkyl), heteroaryl, phenyl, heteroaryloxy or phenyloxy), C_{3-7} cycloalkyl, phenyl or heteroaryl;

wherein any of the immediately foregoing phenyl and heteroaryl moieties are optionally substituted with halo, hydroxy, nitro, S(C₁₋₄ alkyl), S(O)(C₁₋₄ alkyl), S(O)₂(C₁₋₄ alkyl), S(O)₂NH₂, S(O)₂NH(C₁₋₄ alkyl), S(O)₂N(C₁₋₄ alkyl)₂, cyano, C₁₋₄ alkyl, C₁₋₄ alkoxy, C(O)NH₂, C(O)NH(C₁₋₄ alkyl), C(O)N(C₁₋₄ alkyl)₂, CO₂H, CO₂(C₁₋₄ alkyl), NHC(O)(C₁₋₄ alkyl),

- 5 NHS(O)₂(C₁₋₄ alkyl), C(O)(C₁₋₄ alkyl), CF₃ or OCF₃;
R²¹, R²³, R²⁵, R²⁸, R³⁰, R³⁴, R³⁵, R³⁶, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R⁴⁶ and R⁴⁷ may additionally be hydrogen;

or a pharmaceutically acceptable salt thereof or a solvate thereof.

- 10 Certain compounds of the present invention can exist in different isomeric forms (such as enantiomers, diastereomers, geometric isomers or tautomers). The present invention covers all such isomers and mixtures thereof in all proportions.

Suitable salts include acid addition salts such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

- 15 Alkyl groups and moieties are straight or branched chain and, for example, comprise one to six (such as one to four) carbon atoms. Alkyl is, for example, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl or *tert*-butyl. Methyl is sometimes abbreviated to Me hereinbelow.

- 20 Fluoroalkyl includes, for example, one to six, such as one to three, fluorine atoms, and comprises, for example, a CF₃ group. Fluoroalkyl is, for example, CF₃ or CH₂CF₃.

Cycloalkyl is, for example, cyclopropyl, cyclopentyl or cyclohexyl.

Heterocyclyl is, for example, piperidine, piperazine, pyrrolidine, azetidine, tetrahydrofuran, morpholine or thiomorpholine.

Aryl includes phenyl and naphthyl. In one aspect of the invention aryl is phenyl.

- 25 Heteroaryl is, for example, an aromatic 5 or 6 membered ring, optionally fused to one or more other rings, comprising at least one heteroatom selected from the group comprising nitrogen, oxygen and sulphur; or an N-oxide thereof, or an S-oxide or S-dioxide thereof.

- Heteroaryl is, for example, furyl, thienyl (also known as thiophenyl), pyrrolyl, thiazolyl, isothiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, [1,2,4]-triazolyl, pyridinyl, 30 pyrimidinyl, pyrazinyl, indolyl, benzo[b]furyl (also known as benzfuryl), benz[b]thienyl (also known as benzthienyl or benzthiophenyl), indazolyl, benzimidazolyl, benztriazolyl, benzoxazolyl, benzthiazolyl, 1,2,3-benzothiadiazolyl, an imidazopyridinyl (such as imidazo[1,2-a]pyridinyl), thieno[3,2-b]pyridin-6-yl, 1,2,3-benzoxadiazolyl (also known as

benzo[1,2,3]thiadiazolyl), 2,1,3-benzothiadiazolyl, benzofurazan (also known as 2,1,3-benzoxadiazolyl), quinoxaliny, a pyrazolopyridine (for example 1H-pyrazolo[3,4-b]pyridinyl), quinolinyl, isoquinolinyl, a naphthyridinyl (for example [1,6]naphthyridinyl or [1,8]naphthyridinyl), a benzothiazinyl or dibenzothiophenyl (also known as dibenzothienyl);
 5 or an N-oxide thereof, or an S-oxide or S-dioxide thereof.

Aryloxy includes phenoxy.

Heteroaryloxy includes pyridinyloxy and pyrimidinyloxy.

Phenyl(C₁₋₄ alkyl)alkyl is, for example, benzyl, 1-(phenyl)eth-1-yl or 1-(phenyl)eth-2-yl.

10 Heteroaryl(C₁₋₄ alkyl)alkyl is, for example, pyridinylmethyl, pyrimidinylmethyl or 1-(pyridinyl)eth-2-yl.

Phenyl(C₁₋₄ alkoxy) is, for example, benzyloxy or phenylCH(CH₃)O.

Heteroaryl(C₁₋₄ alkoxy) is, for example, pyridinylCH₂O, pyrimidinylCH₂O or pyridinylCH(CH₃)O.

15 In one particular aspect the present invention provides a compound of formula (I) wherein, unless specified otherwise aryl, phenyl and heteroaryl moieties are independently optionally substituted by one or more of halo, hydroxy, nitro, S(C₁₋₆ alkyl), S(O)(C₁₋₆ alkyl), S(O)₂(C₁₋₆ alkyl), S(O)₂NH₂, S(O)₂NH(C₁₋₆ alkyl), S(O)₂N(C₁₋₆ alkyl)₂, cyano, C₁₋₆ alkyl, C₁₋₆ alkoxy, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, C(O)NH₂, C(O)NH(C₁₋₆ alkyl), C(O)N(C₁₋₆ alkyl)₂, C(O)[N-linked heterocyclcyl], CO₂H, CO₂(C₁₋₆ alkyl), NHC(O)(C₁₋₆ alkyl), NHC(O)O(C₁₋₆ alkyl), NHS(O)₂(C₁₋₆ alkyl), CF₃, CHF₂, CH₂F, CH₂CF₃, OCF₃, phenyl, heteroaryl, phenyl(C₁₋₄ alkyl), heteroaryl(C₁₋₄ alkyl), NHC(O)phenyl, NHC(O)heteroaryl, NHC(O)(C₁₋₄ alkyl)phenyl, NHC(O)(C₁₋₄ alkyl)heteroaryl, NHS(O)₂phenyl, NHS(O)₂heteroaryl, NHS(O)₂(C₁₋₄ alkyl)phenyl, NHS(O)₂(C₁₋₄ alkyl)heteroaryl,
 20 NHC(O)NH(C₁₋₆ alkyl), NHC(O)NH(C₃₋₇ cycloalkyl), NHC(O)NHphenyl, NHC(O)NHheteroaryl, NHC(O)NH(C₁₋₄ alkyl)phenyl or NHC(O)NH(C₁₋₄ alkyl)heteroaryl; wherein the foregoing phenyl and heteroaryl groups are optionally substituted by halo, hydroxy, nitro, S(C₁₋₄ alkyl), S(O)(C₁₋₄ alkyl), S(O)₂(C₁₋₄ alkyl), S(O)₂NH₂, S(O)₂NH(C₁₋₄ alkyl), S(O)₂N(C₁₋₄ alkyl)₂, cyano, C₁₋₄ alkyl, C₁₋₄ alkoxy, C(O)NH₂, C(O)NH(C₁₋₄ alkyl),
 25 C(O)N(C₁₋₄ alkyl)₂, CO₂H, CO₂(C₁₋₄ alkyl), NHC(O)(C₁₋₄ alkyl), NHS(O)₂(C₁₋₄ alkyl), CF₃ or OCF₃.

In another aspect the present invention provides a compound of formula (I) wherein, unless specified otherwise aryl, phenyl and heteroaryl moieties are independently optionally

substituted by one or more of halo, hydroxy, nitro, $S(C_{1-4} \text{ alkyl})$, $S(O)(C_{1-4} \text{ alkyl})$, $S(O)_2(C_{1-4} \text{ alkyl})$, $S(O)_2NH_2$, $S(O)_2NH(C_{1-4} \text{ alkyl})$, $S(O)_2N(C_{1-4} \text{ alkyl})_2$, cyano, $C_{1-4} \text{ alkyl}$, $C_{1-4} \text{ alkoxy}$, $C(O)NH_2$, $C(O)NH(C_{1-4} \text{ alkyl})$, CO_2H , $CO_2(C_{1-4} \text{ alkyl})$, $NHC(O)(C_{1-4} \text{ alkyl})$, $NHS(O)_2(C_{1-4} \text{ alkyl})$, CF_3 , CHF_2 , CH_2F , CH_2CF_3 or OCF_3 .

5 In a further aspect of the invention heteroaryl is pyrrolyl, thienyl, imidazolyl, thiazolyl, isoxazolyl, pyridinyl, pyrimidinyl, pyrazinyl or quinolinyl.

In another aspect of the invention R^{10} , R^{13} , R^{15} , R^{16} and R^{18} are hydrogen or $C_{1-4} \text{ alkyl}$ (for example methyl). In yet another aspect R^{10} , R^{13} , R^{15} , R^{16} and R^{18} are hydrogen.

10 In a further aspect of the invention R^{11} , R^{12} , R^{14} , R^{17} , R^{18} and R^{19} are $C_{1-8} \text{ alkyl}$ (optionally substituted by halo, $C_{1-6} \text{ alkoxy}$, $C_{1-6} \text{ haloalkoxy}$, $C_{3-6} \text{ cycloalkyl}$ (optionally substituted by halo), $C_{5-6} \text{ cycloalkenyl}$, $S(O)_2(C_{1-4} \text{ alkyl})$, heteroaryl, phenyl, heteroaryloxy or aryloxy), phenyl, heteroaryl, $C_{3-7} \text{ cycloalkyl}$ (optionally substituted by halo or $C_{1-4} \text{ alkyl}$), $C_{4-7} \text{ cycloalkyl}$ fused to a phenyl ring, $C_{5-7} \text{ cycloalkenyl}$, or, heterocyclyl (itself optionally substituted by oxo, $C(O)(C_{1-6} \text{ alkyl})$, $S(O)_k(C_{1-6} \text{ alkyl})$, halo or $C_{1-4} \text{ alkyl}$); k is 0, 1 or 2; or R^{10} and R^{11} , and/or R^{16} and R^{17} may join to form a 4-, 5- or 6-membered ring which optionally includes a nitrogen, oxygen or sulphur atom, said ring being optionally substituted by $C_{1-6} \text{ alkyl}$ or $C(O)(C_{1-6} \text{ alkyl})$.

20 In yet another aspect of the invention R^{11} , R^{12} , R^{14} , R^{17} and R^{19} are $C_{1-8} \text{ alkyl}$ (optionally substituted by halo (such as fluoro)), phenyl (optionally substituted as recited above), $C_{3-6} \text{ cycloalkyl}$ (optionally substituted by halo (such as fluoro)) or C-linked nitrogen containing heterocyclyl (optionally substituted on the ring nitrogen).

In another aspect of the invention R^1 is $NR^{13}C(O)R^{14}$, wherein R^{13} and R^{14} are as defined above.

25 In yet another aspect of the invention R^{14} is $C_{1-8} \text{ alkyl}$ (optionally substituted by halo (such as fluoro, for example to form CF_3CH_2)), phenyl (optionally substituted as recited above), $C_{3-6} \text{ cycloalkyl}$ (optionally substituted by halo (such as fluoro, for example to form 1,1-difluorocyclohex-4-yl)) or C-linked nitrogen containing heterocyclyl (such as pyran or piperidine, optionally substituted on the ring nitrogen).

30 In a further aspect of the invention heterocyclyl is optionally substituted (such as singly substituted for example on a ring nitrogen atom when present) by $C_{1-6} \text{ alkyl}$ [optionally substituted by phenyl {which itself optionally substituted by halo, $C_{1-4} \text{ alkyl}$, $C_{1-4} \text{ alkoxy}$, cyano, nitro, CF_3 , OCF_3 , $(C_{1-4} \text{ alkyl})C(O)NH$, $S(O)_2NH_2$, $C_{1-4} \text{ alkylthio}$ or $S(O)_2(C_{1-4} \text{ alkyl})$ } or heteroaryl {which itself optionally substituted by halo, $C_{1-4} \text{ alkyl}$, $C_{1-4} \text{ alkoxy}$, cyano, nitro,

CF₃, (C₁₋₄ alkyl)C(O)NH, S(O)₂NH₂, C₁₋₄ alkylthio or S(O)₂(C₁₋₄ alkyl)}, phenyl {optionally substituted by halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, cyano, nitro, CF₃, OCF₃, (C₁₋₄ alkyl)C(O)NH, S(O)₂NH₂, C₁₋₄ alkylthio or S(O)₂(C₁₋₄ alkyl)}, heteroaryl {optionally substituted by halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, cyano, nitro, CF₃, (C₁₋₄ alkyl)C(O)NH, S(O)₂NH₂, C₁₋₄ alkylthio or S(O)₂(C₁₋₄ alkyl)}, S(O)₂NR⁴⁰R⁴¹, C(O)R⁴², C(O)NHR⁴³ or S(O)₂R⁴⁴; wherein R⁴⁰, R⁴¹, R⁴², R⁴³ and R⁴⁴ are, independently, hydrogen or C₁₋₆ alkyl.

In yet another aspect of the invention R¹ is optionally substituted aryl (such as optionally substituted phenyl) or optionally substituted heteroaryl, wherein the optional substituents are as recited above.

In a further aspect of the invention R¹ is optionally substituted heterocyclyl, such as optionally substituted: piperidin-1-yl, piperidin-4-yl, piperazin-1-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, azetidin-1-yl or azetidin-3-yl.

In a still further aspect of the invention the heterocyclyl of R¹ is mono-substituted by C₁₋₆ alkyl, C₃₋₇ cycloalkyl, phenyl {optionally substituted by halo (for example fluoro), C₁₋₄ alkyl (for example methyl), C₁₋₄ alkoxy (for example methoxy), CF₃ or OCF₃}, S(O)₂(C₁₋₄ alkyl) (for example S(O)₂CH₃, S(O)₂CH₂CH₃ or S(O)₂CH(CH₃)₂), S(O)₂(C₁₋₄ fluoroalkyl) (for example S(O)₂CF₃ or S(O)₂CH₂CF₃), S(O)₂phenyl {optionally substituted (such as mono-substituted) by halo (for example chloro), cyano, C₁₋₄ alkyl, C₁₋₄ alkoxy, CF₃, OCF₃, S(O)₂(C₁₋₄ alkyl) (for example S(O)₂CH₃ or S(O)₂CH₂CH₂CH₃) or S(O)₂(C₁₋₄ fluoroalkyl) (for example S(O)₂CH₂CF₃)}, benzyl {optionally substituted by halo (for example chloro or fluoro), C₁₋₄ alkyl, C₁₋₄ alkoxy (for example methoxy), CF₃ or OCF₃}, C(O)H, C(O)(C₁₋₄ alkyl), benzoyl {optionally substituted by halo (for example chloro or fluoro), C₁₋₄ alkyl (for example methyl), C₁₋₄ alkoxy, CF₃ or OCF₃}, C(O)₂(C₁₋₄ alkyl), C(O)NH₂, C(O)NH(C₁₋₄ alkyl) or C(O)NHphenyl {optionally substituted by halo (for example fluoro), C₁₋₄ alkyl, C₁₋₄ alkoxy, CF₃ or OCF₃}. In a still further aspect when said heterocyclyl is a 4-substituted piperidin-1-yl, a 1-substituted piperidin-4-yl, a 1-substituted piperazin-1-yl, a 3-substituted pyrrolidin-1-yl, a 1-substituted pyrrolidin-3-yl, a 3-substituted azetidin-1-yl or a 1-substituted azetidin-3-yl.

In yet another aspect of the invention R² is phenyl or heteroaryl, either of which is optionally substituted by halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, S(O)_n(C₁₋₄ alkyl), nitro, cyano or CF₃; wherein n is 0, 1 or 2, for example 0 or 2.

In a still further aspect R² is optionally substituted (for example unsubstituted or substituted in the 2-, 3-, or 3- and 5- positions) phenyl (such as optionally substituted by halo (such as chloro or fluoro), cyano, methyl, ethyl, methoxy, ethoxy or CF₃), or optionally

substituted (for example unsubstituted or mono-substituted) heteroaryl (such as optionally substituted by halo (such as chloro or fluoro), cyano, methyl, ethyl, methoxy, ethoxy or CF_3).

In another aspect R^2 is optionally substituted (for example unsubstituted or substituted in the 2-, 3-, or 3- and 5- positions) phenyl (such as optionally substituted by halo (for example chloro or fluoro)). For example R^2 is phenyl, 3-fluorophenyl, 3-chlorophenyl, 3,5-difluorophenyl.

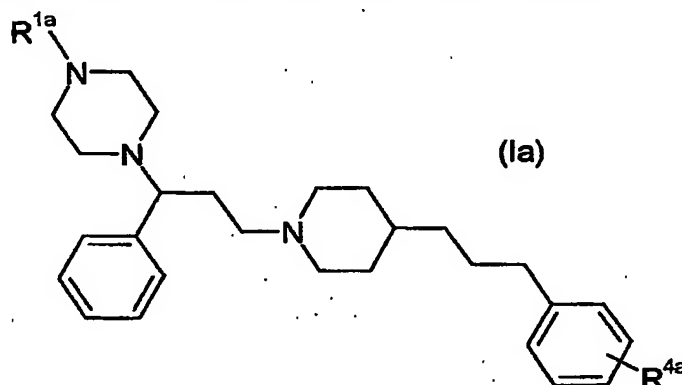
In yet another aspect of the invention R^3 is hydrogen or methyl. In a further aspect of the invention when R^3 is C_{1-4} alkyl (such as methyl) the carbon to which R^3 is attached has the R absolute configuration. In yet another aspect of the invention R^3 is hydrogen.

In a further aspect the present invention provides a compound of the invention wherein R^4 is optionally substituted phenyl.

In a still further aspect of the invention A is absent.

In another aspect of the invention n is 3.

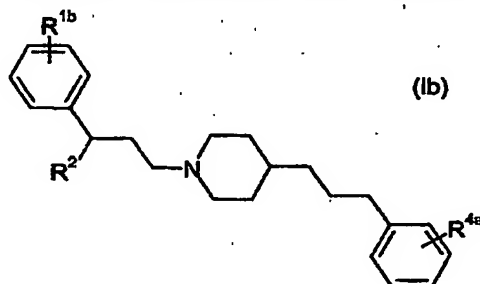
In yet another aspect the present invention provides a compound of formula (Ia):



wherein R^{4a} is as defined for an optional substituents on optionally substituted phenyl (above); and R^{1a} is mono-substituted by C_{1-6} alkyl, C_{3-7} cycloalkyl, phenyl {optionally substituted by halo (for example fluoro), C_{1-4} alkyl (for example methyl), C_{1-4} alkoxy (for example methoxy), CF_3 or OCF_3 }, $\text{S}(\text{O})_2(\text{C}_{1-4}$ alkyl) (for example $\text{S}(\text{O})_2\text{CH}_3$, $\text{S}(\text{O})_2\text{CH}_2\text{CH}_3$ or $\text{S}(\text{O})_2\text{CH}(\text{CH}_3)_2$), $\text{S}(\text{O})_2(\text{C}_{1-4}$ fluoroalkyl) (for example $\text{S}(\text{O})_2\text{CF}_3$ or $\text{S}(\text{O})_2\text{CH}_2\text{CF}_3$), $\text{S}(\text{O})_2$ phenyl {optionally substituted (such as mono-substituted) by halo (for example chloro), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3 , OCF_3 , $\text{S}(\text{O})_2(\text{C}_{1-4}$ alkyl) (for example $\text{S}(\text{O})_2\text{CH}_3$ or $\text{S}(\text{O})_2\text{CH}_2\text{CH}_2\text{CH}_3$) or $\text{S}(\text{O})_2(\text{C}_{1-4}$ fluoroalkyl) (for example $\text{S}(\text{O})_2\text{CH}_2\text{CF}_3$)}, benzyl {optionally substituted by halo (for example chloro or fluoro), C_{1-4} alkyl, C_{1-4} alkoxy (for example methoxy), CF_3 or OCF_3 }, $\text{C}(\text{O})\text{H}$, $\text{C}(\text{O})(\text{C}_{1-4}$ alkyl), benzoyl {optionally substituted

by halo (for example chloro or fluoro), C₁₋₄ alkyl (for example methyl), C₁₋₄ alkoxy, CF₃ or OCF₃, C(O)₂(C₁₋₄ alkyl), C(O)NH₂, C(O)NH(C₁₋₄ alkyl) or C(O)NHphenyl {optionally substituted by halo (for example fluoro), C₁₋₄ alkyl, C₁₋₄ alkoxy, CF₃ or OCF₃}.

In a further aspect the present invention provides a compound of formula (Ib):



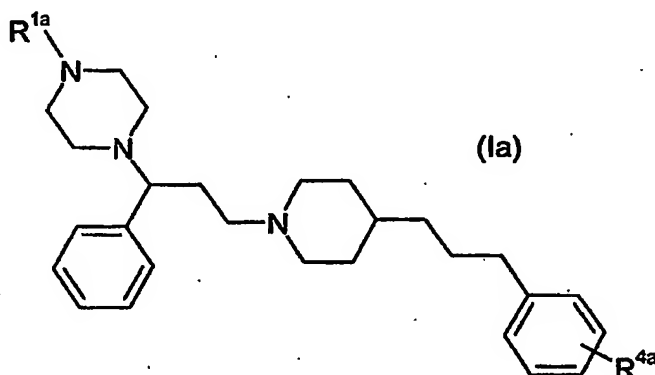
wherein R^{1b} and R^{4a} are, independently, as defined for an optional substituents on optionally substituted phenyl (above); and R² is as defined above.

In a still further aspect the invention provides a compound of formula (I) wherein A is absent; n is 3; R¹ is phenyl substituted by S(O)₂(C₁₋₄ alkyl), or R¹ is piperazin-1-yl 4-substituted by S(O)₂(C₁₋₄ alkyl) or S(O)₂(phenyl); R² and R⁴ are phenyl; and R³ is hydrogen.

The compounds listed in Table I illustrate the invention.

Table I

Table I comprises compounds of formula (Ia):

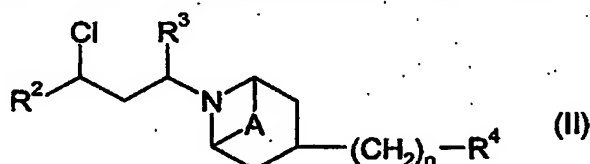


Compound No	R ^{1a}	R ^{4a}
1	benzenesulphonyl	H
2	methanesulphonyl	H
3	ethanesulphonyl	H

In yet another aspect the invention provides each individual compound listed in the table above.

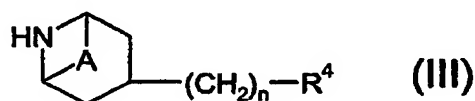
The compounds of formula (I), (Ia) and (Ib) can be prepared as shown below.

- A compound of the invention wherein R^1 is an N-linked optionally substituted
 5 heterocycle can be prepared by reacting a compound of formula (II):

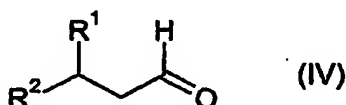


- wherein R^2 , R^3 , R^4 , n and A are as defined above, with a compound R^1H (wherein the H is on a heterocycle ring nitrogen atom) wherein R^1 is as defined above, in the presence of a suitable base (for example a tri(C_{1-6} alkyl)amine such as triethylamine or Hunig's base), in a suitable
 10 solvent (such as a chlorinated solvent, for example dichloromethane) and, for example, at a room temperature (for example 10-30°C), optionally in the presence of sodium iodide.

A compound of the invention, wherein R^3 is hydrogen, can be prepared by coupling a compound of formula (III):



- 15 wherein R^4 , n and A are as defined above, with a compound of formula (IV):



wherein R^1 and R^2 are as defined above, in the presence of $NaBH(OAc)_3$ (wherein Ac is $C(O)CH_3$) in a suitable solvent (such as a chlorinated solvent, for example dichloromethane) at room temperature (for example 10-30°C).

- 20 Alternatively, compounds of the invention can be prepared according to Schemes 1-7 (below).

- Alternatively, compounds of the invention can be prepared by using or adapting methods described in WO01/87839, EP-A1-1013276, WO00/08013, WO99/38514, WO99/04794, WO00/76511, WO00/76512, WO00/76513, WO00/76514, WO00/76972 or
 25 US 2002/0094989.

The starting materials for these processes are either commercially available or can be prepared by literature methods, adapting literature methods or by following or adapting Methods herein described.

5 In a still further aspect the invention provides processes for preparing the compounds of formula (I), (Ia) and (Ib). Many of the intermediates in the processes are novel and these are provided as further features of the invention.

10 The compounds of the invention have activity as pharmaceuticals, in particular as modulators (such as agonists, partial agonists, inverse agonists or antagonists) of chemokine receptor (especially CCR5) activity, and may be used in the treatment of autoimmune, inflammatory, proliferative or hyperproliferative diseases, or immunologically-mediated diseases (including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS)).

15 The compounds of the present invention are also of value in inhibiting the entry of viruses (such as human immunodeficiency virus (HIV)) into target cells and, therefore, are of value in the prevention of infection by viruses (such as HIV), the treatment of infection by viruses (such as HIV) and the prevention and/or treatment of acquired immune deficiency syndrome (AIDS).

20 According to a further feature of the invention there is provided a compound of the formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof or a solvate thereof, for use in a method of treatment of a warm blooded animal (such as man) by therapy (including prophylaxis).

25 According to a further feature of the present invention there is provided a method for modulating chemokine receptor activity (especially CCR5 receptor activity) in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof or a solvate thereof.

30 The present invention also provides the use of a compound of the formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof or a solvate thereof, as a medicament, especially a medicament for the treatment of transplant rejection, respiratory disease, psoriasis or rheumatoid arthritis (especially rheumatoid arthritis). [Respiratory disease is, for example, COPD, asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)} or rhinitis {acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa,

hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; and is particularly asthma or rhinitis].

5 In another aspect the present invention provides the use of a compound of the formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof or a solvate thereof, in the manufacture of a medicament for use in therapy (for example modulating chemokine receptor activity (especially CCR5 receptor activity (especially rheumatoid arthritis)) in a warm blooded animal, such as man).

10 The invention also provides a compound of the formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof or a solvate thereof, for use as a medicament, especially a medicament for the treatment of rheumatoid arthritis.

In another aspect the present invention provides the use of a compound of the formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof or a solvate thereof, in the
15 manufacture of a medicament for use in therapy (for example modulating chemokine receptor activity (especially CCR5 receptor activity (especially rheumatoid arthritis)) in a warm blooded animal, such as man).

The invention further provides the use of a compound of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the
20 treatment of:

- (1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)); bronchitis {such as eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung or
25 idiopathic interstitial pneumonia;
- 30 (2) (bone and joints) arthrides including rheumatic, infectious, autoimmune, seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behçet's disease, Sjogren's syndrome or systemic sclerosis;

- (3) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczmatous dermatides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, Alopecia areata or vernal conjunctivitis;
- 5 (4) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);
- 10 (5) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea; or chronic graft versus host disease; and/or
- 15 (6) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), Lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), Peridontal disease, Sezary syndrome, idiopathic thrombocytopenia pupura or disorders of the menstrual cycle;
- in a warm blooded animal, such as man.

20 The present invention further provides a method of treating a chemokine mediated disease state (especially a CCR5 mediated disease state) in a warm blooded animal, such as man, which comprises administering to a mammal in need of such treatment an effective amount of a compound of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof or solvate thereof.

25 In order to use a compound of the invention, or a pharmaceutically acceptable salt thereof or solvate thereof, for the therapeutic treatment of a warm blooded animal, such as man, in particular modulating chemokine receptor (for example CCR5 receptor) activity, said ingredient is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

30 Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof or a solvate thereof (active ingredient), and a pharmaceutically acceptable adjuvant, diluent or carrier. In a further aspect the present invention provides a process for the preparation of said composition which comprises mixing

active ingredient with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active
5 ingredient, all percentages by weight being based on total composition.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by topical (such as to the lung and/or airways or to the skin), oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art into
10 the form of, for example, aerosols, dry powder formulations, tablets, capsules, syrups, powders, granules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, drops and sterile injectable aqueous or oily solutions or suspensions.

A suitable pharmaceutical composition of this invention is one suitable for oral
15 administration in unit dosage form, for example a tablet or capsule which contains between 0.1mg and 1g of active ingredient.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection.

Each patient may receive, for example, an intravenous, subcutaneous or intramuscular
20 dose of 0.01mgkg^{-1} to 100mgkg^{-1} of the compound, preferably in the range of 0.1mgkg^{-1} to 20mgkg^{-1} of this invention, the composition being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient will receive a daily oral dose which is
25 approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

The following illustrate representative pharmaceutical dosage forms containing the compound of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof or a solvent thereof (hereafter Compound X), for therapeutic or prophylactic use in humans:

(a)

<u>Tablet I</u>	<u>mg/tablet</u>
Compound X	100
Lactose Ph.Eur.	179
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(b)

<u>Tablet II</u>	<u>mg/tablet</u>
Compound X	50
Lactose Ph.Eur.	229
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

5 (c)

<u>Tablet III</u>	<u>mg/tablet</u>
Compound X	1.0
Lactose Ph.Eur.	92
Croscarmellose sodium	4.0
Polyvinylpyrrolidone	2.0
Magnesium stearate	1.0

(d)

<u>Capsule</u>	<u>mg/capsule</u>
Compound X	10
Lactose Ph.Eur.	389
Croscarmellose sodium	100
Magnesium stearate	1.0

(e)

<u>Injection I</u>	<u>(50 mg/ml)</u>
Compound X	5.0% w/v
Isotonic aqueous solution	to 100%

5 Buffers, pharmaceutically-acceptable cosolvents such as polyethylene glycol, polypropylene glycol, glycerol or ethanol or complexing agents such as hydroxy-propyl β -cyclodextrin may be used to aid formulation.

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

10 The invention will now be illustrated by the following non-limiting Examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius ($^{\circ}\text{C}$); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25 $^{\circ}\text{C}$;

15 (ii) organic solutions were dried over anhydrous magnesium sulfate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mm Hg) with a bath temperature of up to 60 $^{\circ}\text{C}$;

20 (iii) chromatography unless otherwise stated means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates; where a "Bond Elut" column is referred to, this means a column containing 10g or 20g of silica of 40 micron particle size, the silica being contained in a 60ml disposable syringe and supported by a porous disc, obtained from Varian, Harbor City, California, USA under the name "Mega Bond Elut SP". Where an "IsoluteTM SCX column" is referred to, this means a column containing benzenesulphonic acid (non-endcapped) obtained from International Sorbent Technology Ltd., 1st House, Duffryn Industrial Estate, Ystrad Mynach, Hengoed, Mid Glamorgan, UK. Where "ArgonautTM PS-*tris*-amine scavenger resin" is referred to, this means a *tris*-(2-aminoethyl)amine polystyrene resin obtained from Argonaut Technologies Inc., 887 Industrial Road, Suite G, San Carlos, California, USA.

25 (iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) yields, when given, are for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vi) when given, ^1H NMR data is quoted and is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using perdeuterio DMSO (CD_3SOCD_3) as the solvent unless otherwise stated; coupling constants (J) are given in Hz;

(vii) chemical symbols have their usual meanings; SI units and symbols are used;

(viii) solvent ratios are given in percentage by volume;

(ix) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (APCI) mode using a direct exposure probe; where indicated ionisation was effected by electrospray (ES); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(\text{M}+\text{H})^+$;

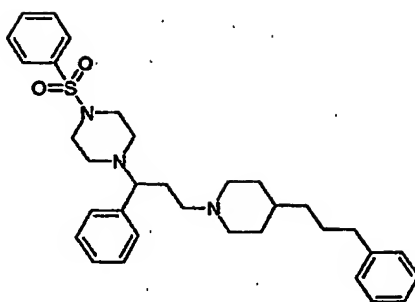
(x) LCMS characterisation was performed using a pair of Gilson 306 pumps with Gilson 233 XL sampler and Waters ZMD4000 mass spectrometer. The LC comprised water symmetry 4.6x50 column C18 with 5 micron particle size. The eluents were: A, water with 0.05% formic acid and B, acetonitrile with 0.05% formic acid. The eluent gradient went from 95% A to 95% B in 6 minutes. Where indicated ionisation was effected by electrospray (ES); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(\text{M}+\text{H})^+$ and

(xi) the following abbreviations are used:

DMF	<i>N,N</i> -dimethylformamide; and,
THF	tetrahydrofuran.

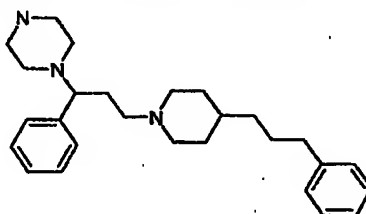
Example 1

This Example illustrates the preparation of *N*-(3-phenyl-3-[4-benzenesulphonylpiperazin-1-yl]propyl)-4-(3-phenylpropyl)piperidine (Compound No. 1, Table I).



Benzenesulphonyl chloride (63 μ l) was added dropwise to a solution of N-(3-phenyl-3-piperazin-1-yl)propyl-4-(3-phenylpropyl)piperidine (0.2g) and triethylamine (0.14ml) in dichloromethane (10ml) maintained at 0°C. The mixture was allowed to warm to room temperature and was stirred for 1 hour. The reaction mixture was washed successively with water (20ml) and brine (20ml) and was dried. The residue obtained on removal of the solvent was chromatographed on a 20g silica Bond-Elut column eluting with a solvent gradient ethyl acetate-20% methanol/ethyl acetate to give the title compound, yield 170 mg. MH^+ 546. NMR ($CDCl_3$): 1.2 (m, 5H), 1.6 (m, 4H), 1.8 (m, 3H), 2.0-2.2 (m, 2H), 2.5 (m, 4H), 2.6 (t, 2H), 2.8 (t, 2H), 3.0 (bs, 4H), 3.3 (m, 1H), 7.2 (m, 4H), 7.25 (m, 5H), 7.5 (m, 3H), 7.7 (d, 2H).

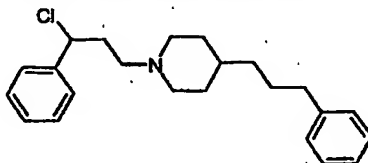
N-(3-phenyl-3-piperazin-1-ylpropyl)-4-(3-phenylpropyl)piperidine.



To a solution of N-tert-butoxycarbonylpiperazine (0.425g) in dichloromethane (50ml) was added triethylamine (0.63 ml), N-(3-chloro-3-phenylpropyl)-4-(3-phenylpropyl)piperidine (0.81g) and sodium iodide (0.1g) and the mixture was stirred for 20 hours. The reaction mixture was washed successively with water (25ml) and brine (25ml) and dried. The residue obtained on removal of the solvent was chromatographed on a 50g silica Bond Elut column to give the N-(3-phenyl-3-[tert-butoxycarbonylpiperazin-1-yl]propyl)-4-(3-phenylpropyl)piperidine (MH^+ 506) which was dissolved in dichloromethane to which trifluoroacetic anhydride (5 ml) was added. The mixture was stirred for 30 minutes and the solvent was removed under reduced pressure. The residue was dissolved in 2M sodium hydroxide and this solution was extracted with dichloromethane (3X10 ml). The combined

dichloromethane extracts were dried and the solvent removed to give the title compound, yield 0.84g, MH^+ 406.

N-(3-chloro-3-phenylpropyl)-4-(3-phenylpropyl)piperidine

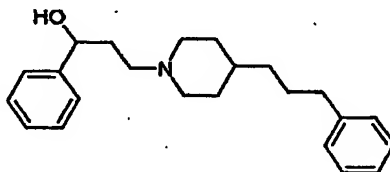


5

Triethylamine (1.04ml) was added to a solution of N-(3-hydroxy-3-phenylpropyl)-4-(3-phenylpropyl)piperidine (1.27g) in dichloromethane (30ml) followed by methanesulphonyl chloride (0.29ml) and the mixture was stirred for 18 hours at room temperature. The reaction mixture was washed successively with water (25ml) and brine (25ml) and the dichloromethane solution was dried. The residue obtained after removal of the solvent was chromatographed on a 50g silica Bond Elut column eluted with a solvent gradient of ethyl acetate-30% methanol/ethyl acetate to give the title compound, yield 0.81g, MH^+ 356.

10

N-(3-hydroxy-3-phenylpropyl)-4-(3-phenylpropyl)piperidine

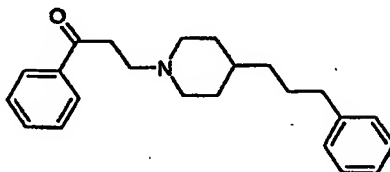


15

Sodium borohydride (180mg) was added in portions to a solution of N-(3-oxo-3-phenylpropyl)-4-(3-phenylpropyl)piperidine (1.44g) in ethanol (40ml) at 0 °C, the mixture was allowed to warm to room temperature and was stirred for 18 hours. The reaction mixture was evaporated to dryness and the residue was dissolved in dichloromethane (30ml) and this solution was washed with water (25ml) and dried. Removal of the solvent gave the title compound as an oil, yield 1.27g, MH^+ 338.

20

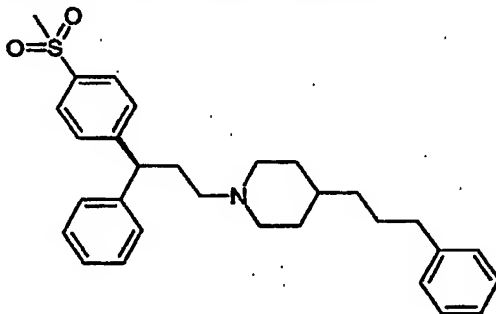
N-(3-oxo-3-phenylpropyl)-4-(3-phenylpropyl)piperidine



A solution of 4-(3-phenylpropyl)piperidine (0.985g) in DMF (2ml) was added to a mixture of 3-chloropropiophenone (0.86g) and potassium carbonate (1.34g) in DMF (20ml) and the mixture was stirred for 1 hour. The reaction mixture was evaporated to dryness and the residue was dissolved in dichloromethane (40ml). The dichloromethane solution was washed with water (20ml) and dried. Removal of the solvent gave the title compound as an orange oil which was used without further purification. Yield 1.44g, MH^+ 336.

Example 2

This Example illustrates the preparation of (S) N-(3-phenyl-3-[4-methanesulphonylphenyl]propyl)-4-(3-phenylpropyl)piperidine.

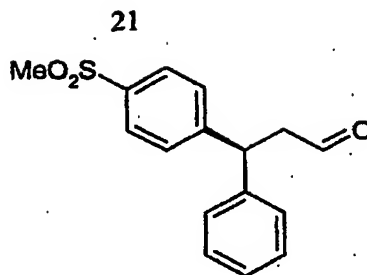


MP-Triacetoxyborohydride (640mg) (Argonaut Technologies Inc) was added to a solution of (S)-3-phenyl-3-(4-methanesulphonylphenyl)propionaldehyde (150mg, Method A) and 4-(3-phenylpropyl)piperidine (127mg) in dichloromethane (10ml) and the mixture was stirred for 16 hours. The mixture was poured onto a 20g silica Bond-Elut column and eluted with a solvent gradient (ethyl acetate – 30% methanol/ethyl acetate) to give the title compound as a gum, yield 70mg; MH^+ 476.

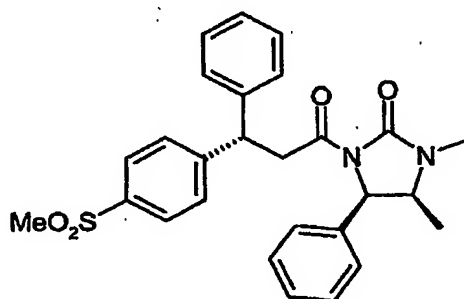
1H NMR($CDCl_3$) : 1.2 (m, 5H), 1.6 (m, 4H), 1.8 (m, 3H), 2.2 (M, 4H), 2.6 (m, 2H), 2.8 (m, 2H), 3.0 (s, 3H), 4.1 (m, 1H), 7.2-7.3 (m, 10H), 7.4 (d, 2H), 7.8 (d, 2H).

Method A

(S)-3-Phenyl-3-(4-methanesulphonylphenyl)propionaldehyde



Step 1: Preparation of (4*R*, 5*S*)-1-[(*S*)-3-(4-methanesulfonyl-phenyl)-3-phenyl-propionyl]-3,4-dimethyl-5-phenyl-imidazolidin-2-one



5 To a mixture of copper (I) iodide (960mg, 5.0mmol) and THF (20mL) was added *N,N,N',N'*-tetramethylethylenediamine (0.83mL, 5.5mmol) and the resulting mixture was stirred at room temperature for 10min. then cooled to -78°C . Phenylmagnesium bromide (5.0mL, 1M in THF, 5.0mmol) was added and the resulting mixture stirred at -78°C for 15min. A solution of di-*n*-butylboron triflate (3.0mL, 1M in diethyl ether, 3.0mmol) and (*E*)-
 10 (4*R*, 5*S*)-1-(3-[4-methanesulfonylphenyl]acryloyl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one (Step 4 below, 1.0g, 2.51mmol) in THF (15mL) was added and the resulting mixture was stirred whilst allowing to warm to room temperature for 18h. The reaction mixture was washed with saturated aqueous ammonium chloride, water and brine, dried (MgSO_4) and evaporated. The residue was purified by eluting through a 20g Bond Elut with gradient of
 15 isohexane to ethyl acetate giving the sub-titled compound (1.49g, 100%); NMR (CDCl_3): 0.78 (d, 3H), 2.82 (s, 3H), 3.00 (s, 3H), 3.78 (dd, 1H), 3.80 (m, 1H), 3.98 (dd, 1H), 4.72 (m, 1H), 5.19 (d, 1H), 6.99 (m, 2H), 7.22 (m, 8H), 7.48 (d, 2H), 7.79 (d, 2H); MS: 477 (MH⁺).

Step 2: Preparation of (*S*)-3-phenyl-3-(4-methanesulfonylphenyl)propan-1-ol

20 To a solution of (4*R*, 5*S*)-1-[(*S*)-3-(4-methanesulfonyl-phenyl)-3-phenyl-propionyl]-3,4-dimethyl-5-phenyl-imidazolidin-2-one (846mg, 1.78mmol) in THF (20mL) at 0°C was added lithium aluminium hydride (3.6mL, 1M in THF, 3.6mmol) and the resulting mixture was stirred for 15min. The reaction was quenched by the addition of 2M aqueous sodium

hydroxide. The phases were separated and the organic phase pre-absorbed onto a Bond Elut and eluted with a gradient of isohexane to ethyl acetate giving the sub-titled compound as a white solid (285mg, 55%); NMR (CDCl₃): 1.63 (br s, 1H), 2.33 (m, 2H), 3.00 (s, 3H), 3.59 (t, 2H), 4.28 (t, 1H), 7.23 (m, 5H), 7.43 (d, 2H), 7.82 (d, 2H).

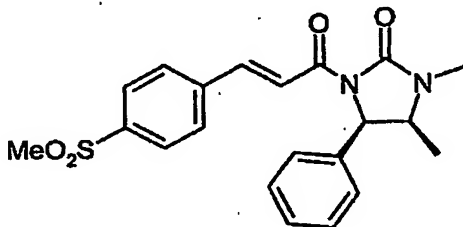
5

Step 3: Preparation of the title compound

To a solution of (*S*)-3-phenyl-3-(4-methanesulfonylphenyl)propan-1-ol (244mg, 0.84mmol) in DCM (5mL) was added Dess-Martin periodinane (392mg, 0.92mmol) and the resulting mixture was stirred at room temperature for 1.5h. The mixture was washed with 2M aqueous sodium hydroxide (2 x 10mL), dried and evaporated to give the title compound.

10

Step 4: Preparation of *E*-(4*R*, 5*S*)-1-(3-[4-Methanesulphonylphenyl]acryloyl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one



15

To a stirred solution of 3-(4-methanesulphonylphenyl)acrylic acid (7.14g, 31.5mmol) in DCM (10mL) was added thionyl chloride (3mL, 34.7mmol) dropwise and the resulting mixture was stirred at room temperature for 18h. To this solution was added DIPEA (5.04mL, 28.9mmol) dropwise at room temperature. The resulting solution was added to a stirred solution of (4*R*, 5*S*)-3,4-dimethyl-5-phenyl-imidazolidin-2-one (5.0g, 26.3mmol) in DCM (20mL) and DIPEA (4.58mL, 26.9mmol) and the resulting mixture stirred at room temperature for 4h. The mixture was washed with water and brine, pre-absorbed onto a Bond Elut and eluted with a gradient of isohexane to ethyl acetate giving the title compound as a solid (7.61g, 73%); NMR (CDCl₃): 0.84 (d, 3H), 2.89 (s, 3H), 3.04 (s, 3H), 3.98 (m, 1H), 5.42 (d, 1H), 7.20 (m, 2H), 7.32 (m, 3H), 7.69 (d, 1H), 7.74 (d, 2H), 7.93 (d, 2H), 8.31 (d, 1H); MS: 399 (MH⁺).

20

25

EXAMPLE 3

The ability of compounds to inhibit the binding of RANTES was assessed by an *in vitro* radioligand binding assay. Membranes were prepared from Chinese hamster ovary cells which expressed the recombinant human CCR5 receptor. These membranes were incubated with 0.1nM iodinated RANTES, scintillation proximity beads and various concentrations of the compounds of the invention in 96-well plates. The amount of iodinated RANTES bound to the receptor was determined by scintillation counting. Competition curves were obtained for compounds and the concentration of compound which displaced 50% of bound iodinated RANTES was calculated (IC_{50}). Preferred compounds of formula (I) have an IC_{50} of less than 50 μ M.

EXAMPLE 4

The ability of compounds to inhibit the binding of MIP-1 α was assessed by an *in vitro* radioligand binding assay. Membranes were prepared from Chinese hamster ovary cells which expressed the recombinant human CCR5 receptor. These membranes were incubated with 0.1nM iodinated MIP-1 α , scintillation proximity beads and various concentrations of the compounds of the invention in 96-well plates. The amount of iodinated MIP-1 α bound to the receptor was determined by scintillation counting. Competition curves were obtained for compounds and the concentration of compound which displaced 50% of bound iodinated MIP-1 α was calculated (IC_{50}). Preferred compounds of formula (I) have an IC_{50} of less than 50 μ M.

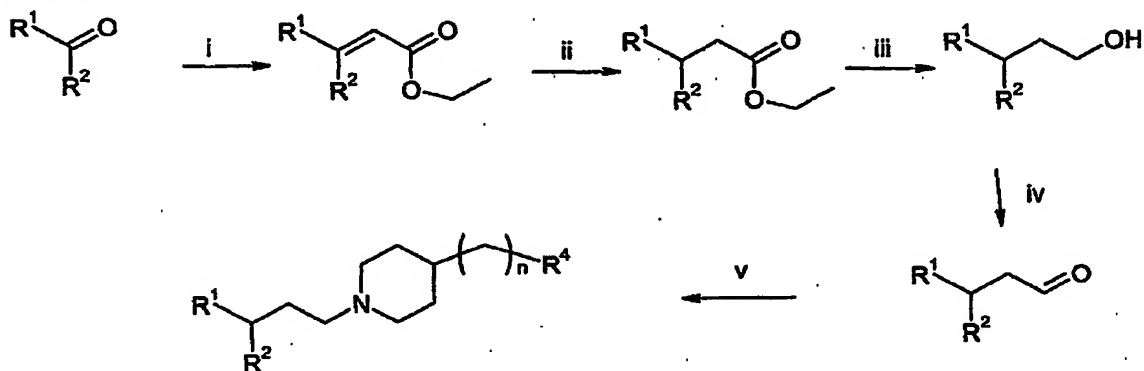
Results from this test for certain compounds of the invention are presented in Table II. In Table II the results are presented as Pic50 values. A Pic50 value is the negative log (to base 10) of the IC_{50} result, so an IC_{50} of 1 μ M (that is 1×10^{-6} M) gives a Pic50 of 6. If a compound was tested more than once then the data below is an average of the probative tests results.

Table II

Compound number	Pic50
3	7.01

Scheme 1

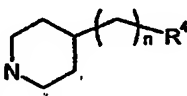
To prepare compounds of the invention, for example wherein R^1 is aryl or C-linked piperidine.



5

- i Wittig reaction (eg LHDMS, triethylphosphonoacetate)
- ii Catalytic hydrogenation (eg H_2 , 10% Pd/C)
- iii Reduction (eg lithium aluminium hydride)
- iv Oxidation (eg Dess-Martin oxidation)

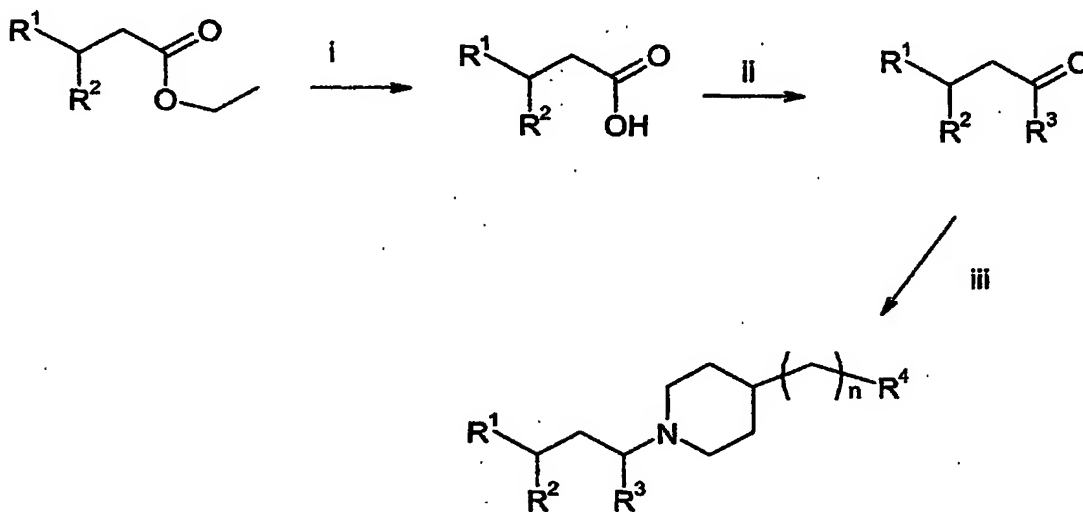
v

reductive amination with  (eg using sodium triacetoxyborohydride)

10

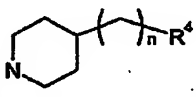
Scheme 2

To prepare compounds of the invention, for example wherein R^1 is aryl or C-linked piperidine.



5

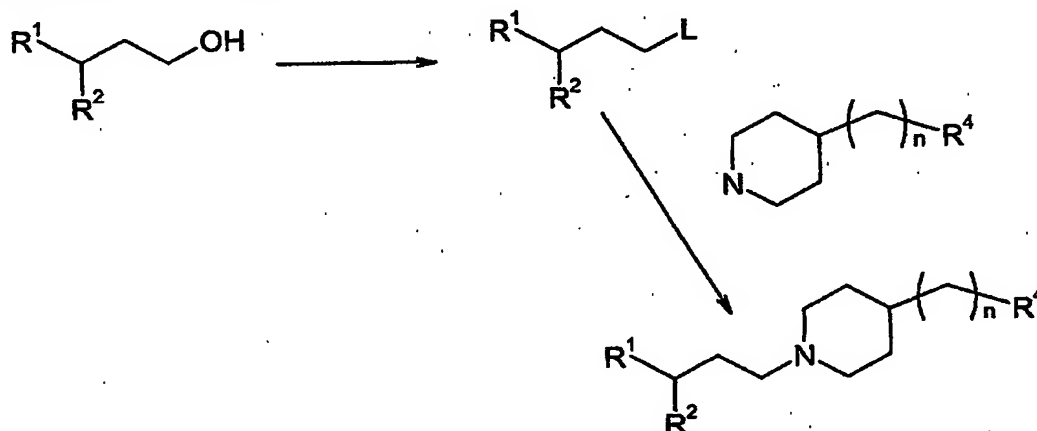
- i Base hydrolysis (eg LiOH, MeOH/H₂O)
- ii MeMgCl, R^3MgBr , Et₂O

- iii reductive amination  in presence of titanium tetraisopropoxide (eg using sodium triacetoxyborohydride)

10

Scheme 3

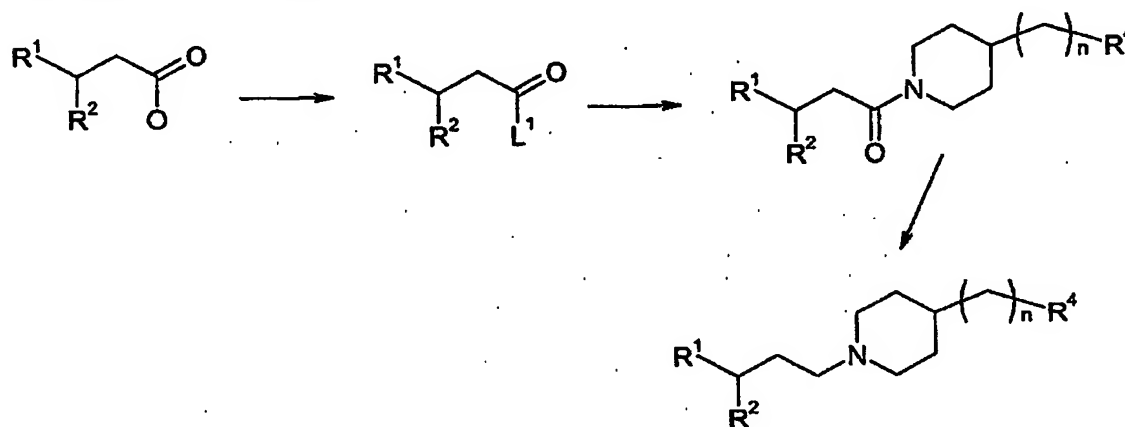
To prepare compounds of the invention, for example wherein R^1 is aryl, heteroaryl, heterocyclyl or $NR^{13}C(O)R^{14}$.



5 wherein L is an activated group such as halogen, mesylate, tosylate or triflate.

Scheme 4

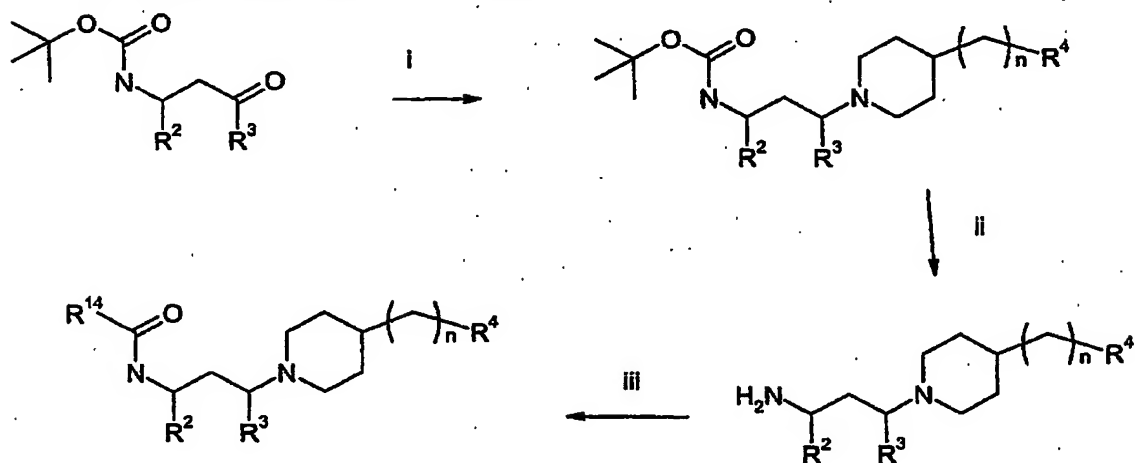
To prepare compounds of the invention, for example wherein R^1 is aryl, heteroaryl, heterocyclyl or $NR^{13}C(O)R^{14}$.



L^1 is a halogen, activated ester or complex formed with a carbodiimide.

Scheme 5

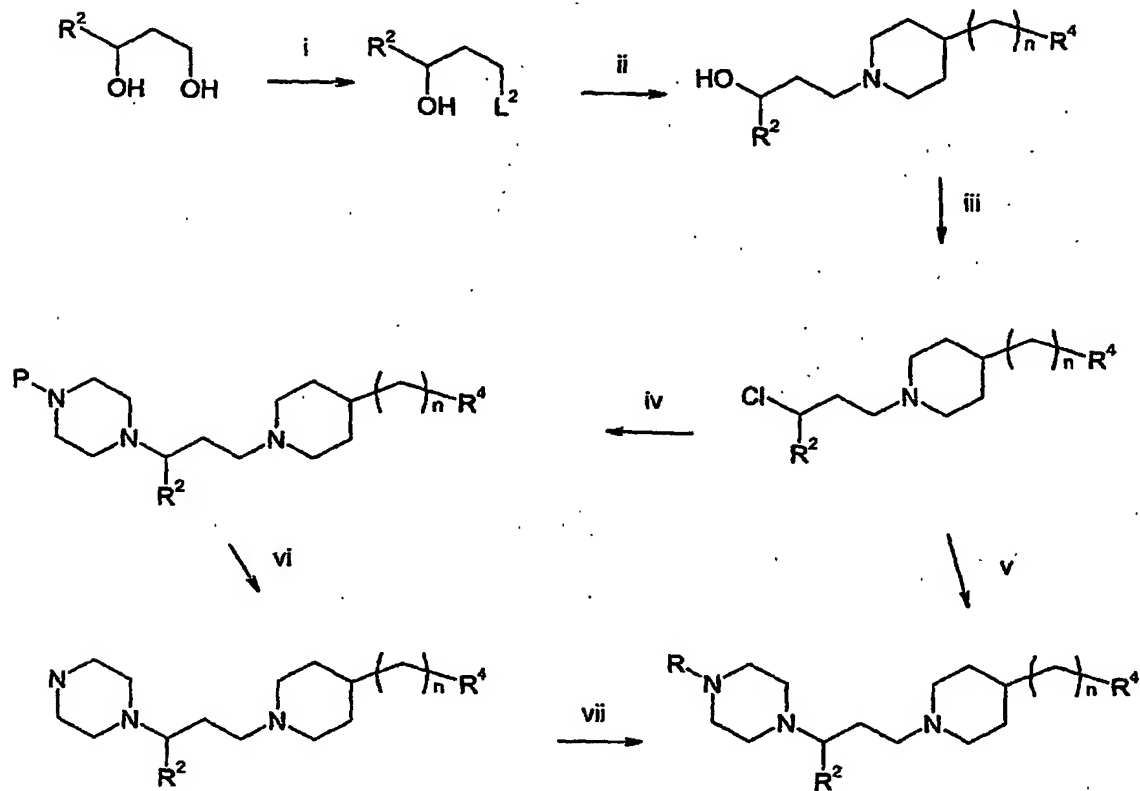
To prepare compounds of the invention, for example wherein R^1 is $NR^{13}C(O)R^{14}$.



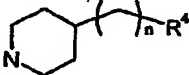
- 5
- i reductive amination (if R^3 is H can use sodium triacetoxyborohydride; if R^3 is alkyl can use titanium tetra-isopropoxide and sodium triacetoxyborohydride)
 - ii Deprotection (eg TFA)
 - iii amide bond formation (eg acid chloride, active ester or carbodiimide mediated)

Scheme 6

To prepare compounds of the invention, for example wherein R^1 is piperazine



- i Conversion of an OH to a leaving group (eg tosyl chloride (L^2 is Tosylate) or mesyl chloride (L^2 is Mesylate))

- ii displacement reaction with  (eg in presence of triethylamine)

- iii Mesyl chloride, DCM 0°C

- iv Displacement reaction with mono-protected piperazine (P = protecting group)

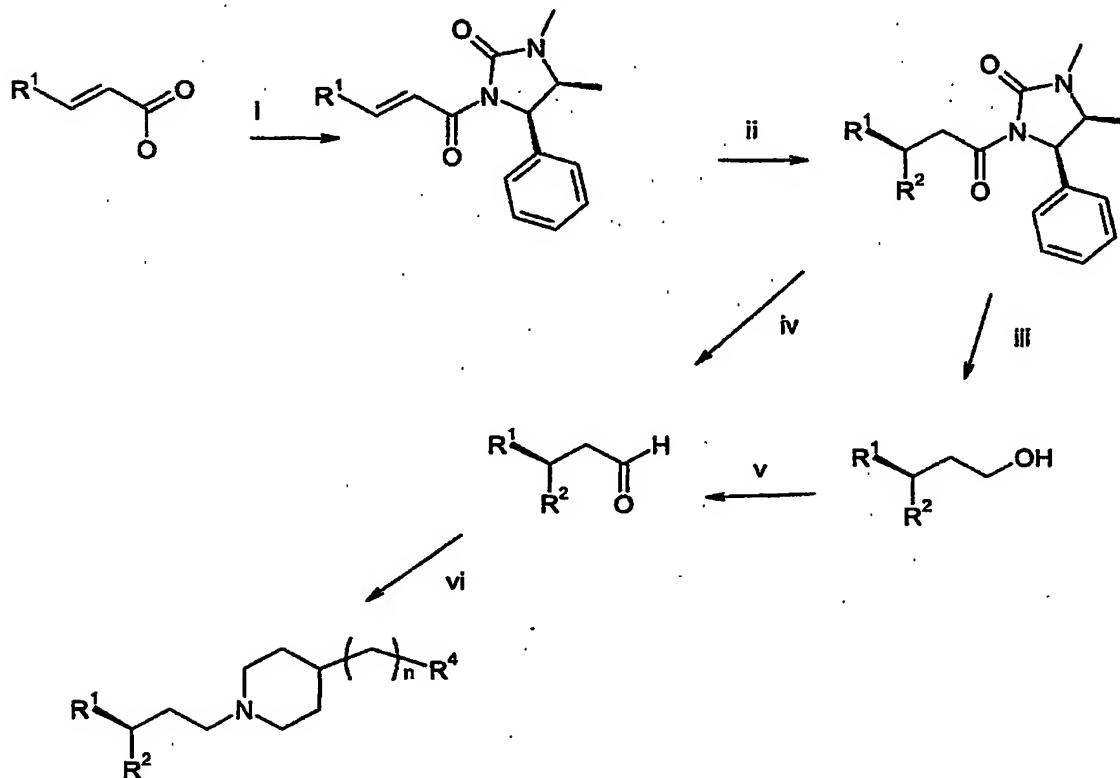
- v Displacement reaction with R substituted piperazine

- vi Deprotection (TFA for Boc, hydrogenation for Cbz)

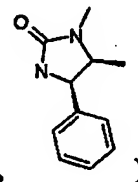
- vii Depending on R, acylation, sulfonylation, alkylation, reductive amination

Scheme 7

To prepare compounds of the invention, for example wherein R^1 is aryl or piperidine.

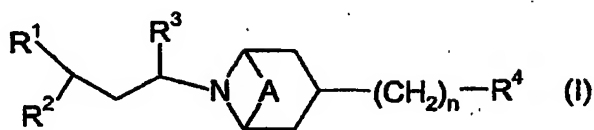


- i activation of acid group and coupling with chiral auxiliary (eg SOCl_2 ,
 5 ii 1,4-addition of organocuprate (eg R^2MgBr , Cu(I)I , TMEDA, di-butylboron triflate)
 iii reduction (eg LAH)
 iv Dibal
 v Oxidation (eg Dess-Martin reagent)
 vi reductive amination (eg with sodium triacetoxyborohydride)



CLAIMS

1. A compound of formula (I):



5 wherein

A is absent or is (CH₂)₂;

R¹ is C₁₋₈ alkyl, C(O)NR¹⁰R¹¹, C(O)₂R¹², NR¹³C(O)R¹⁴, NR¹⁵C(O)NR¹⁶R¹⁷, NR¹⁸C(O)₂R¹⁹ heterocyclyl (for example piperidine, piperazine, pyrrolidine or azetidine), aryl or heteroaryl;

10 R¹⁰, R¹³, R¹⁵, R¹⁶ and R¹⁸ are hydrogen or C₁₋₆ alkyl;

R¹¹, R¹², R¹⁴, R¹⁷ and R¹⁹ are C₁₋₈ alkyl (optionally substituted by halo, hydroxy, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl (optionally substituted by halo), C₅₋₆ cycloalkenyl, S(C₁₋₄ alkyl), S(O)(C₁₋₄ alkyl), S(O)₂(C₁₋₄ alkyl), heteroaryl, aryl, heteroaryloxy or aryloxy), aryl, heteroaryl, C₃₋₇ cycloalkyl (optionally substituted by halo or C₁₋₄ alkyl), C₄₋₇ cycloalkyl fused to a phenyl ring, C₅₋₇ cycloalkenyl, or, heterocyclyl (itself optionally substituted by oxo, C(O)(C₁₋₆ alkyl), S(O)_k(C₁₋₆ alkyl), halo or C₁₋₄ alkyl); or R¹¹, R¹², R¹⁴ and R¹⁷ can also be hydrogen;

15 or R¹⁰ and R¹¹, and/or R¹⁶ and R¹⁷ may join to form a 4-, 5- or 6-membered ring which optionally includes a nitrogen, oxygen or sulphur atom, said ring being optionally substituted by C₁₋₆ alkyl, S(O)_k(C₁₋₆ alkyl) or C(O)(C₁₋₆ alkyl);

20 R² C₁₋₆ alkyl, phenyl, heteroaryl or C₃₋₇ cycloalkyl;

R³ H or C₁₋₄ alkyl;

R⁴ is aryl or heteroaryl;

n is 2, 3 or 4;

25 unless specified otherwise aryl, phenyl and heteroaryl moieties are independently optionally substituted by one or more of halo, cyano, nitro, hydroxy, OC(O)NR²⁰R²¹, NR²²R²³, NR²⁴C(O)R²⁵, NR²⁶C(O)NR²⁷R²⁸, S(O)₂NR²⁹R³⁰, NR³¹S(O)₂R³², C(O)NR³³R³⁴, CO₂R³⁶, NR³⁷CO₂R³⁸, S(O)_qR³⁹, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy(C₁₋₆)alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, phenyl, phenyl(C₁₋₄)alkyl, phenoxy, phenylthio, phenylS(O), phenylS(O)₂, phenyl(C₁₋

4)alkoxy, heteroaryl, heteroaryl(C₁₋₄)alkyl, heteroaryloxy or heteroaryl(C₁₋₄)alkoxy; wherein any of the immediately foregoing phenyl and heteroaryl moieties are optionally substituted with halo, hydroxy, nitro, S(C₁₋₄ alkyl), S(O)(C₁₋₄ alkyl), S(O)₂(C₁₋₄ alkyl), S(O)₂NH₂, S(O)₂NH(C₁₋₄ alkyl), S(O)₂N(C₁₋₄ alkyl)₂, cyano, C₁₋₄ alkyl, C₁₋₄ alkoxy, C(O)NH₂, C(O)NH(C₁₋₄ alkyl), C(O)N(C₁₋₄ alkyl)₂, CO₂H, CO₂(C₁₋₄ alkyl), NHC(O)(C₁₋₄ alkyl), NHS(O)₂(C₁₋₄ alkyl), CF₃ or OCF₃;

unless otherwise stated heterocyclyl is optionally substituted by C₁₋₆ alkyl [optionally substituted by phenyl {which itself optionally substituted by halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, cyano, nitro, CF₃, OCF₃, (C₁₋₄ alkyl)C(O)NH, S(O)₂NH₂, C₁₋₄ alkylthio, S(O)(C₁₋₄ alkyl) or S(O)₂(C₁₋₄ alkyl)} or heteroaryl {which itself optionally substituted by halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, cyano, nitro, CF₃, (C₁₋₄ alkyl)C(O)NH, S(O)₂NH₂, C₁₋₄ alkylthio, S(O)(C₁₋₄ alkyl) or S(O)₂(C₁₋₄ alkyl)}], phenyl {optionally substituted by halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, cyano, nitro, CF₃, OCF₃, (C₁₋₄ alkyl)C(O)NH, S(O)₂NH₂, C₁₋₄ alkylthio, S(O)(C₁₋₄ alkyl) or S(O)₂(C₁₋₄ alkyl)}, heteroaryl {optionally substituted by halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, cyano, nitro, CF₃, (C₁₋₄ alkyl)C(O)NH, S(O)₂NH₂, C₁₋₄ alkylthio, S(O)(C₁₋₄ alkyl) or S(O)₂(C₁₋₄ alkyl)}, S(O)₂NR⁴⁰R⁴¹, C(O)R⁴², C(O)₂(C₁₋₆ alkyl) (such as tert-butoxycarbonyl), C(O)₂(phenyl(C₁₋₂ alkyl)) (such as benzyloxycarbonyl), C(O)NHR⁴³, S(O)₂R⁴⁴, NHS(O)₂NHR⁴⁵, NHC(O)R⁴⁶, NHC(O)NHR⁴⁷ or NHS(O)₂R⁴⁸, provided none of these last four substituents is linked to a ring nitrogen;

k, l, p and q are, independently, 0, 1 or 2;

R²⁰, R²², R²⁴, R²⁶, R²⁷, R²⁹, R³¹, R³³, R³⁷ and R⁴⁰ are, independently, hydrogen or C₁₋₆ alkyl;

R²¹, R²³, R²⁵, R²⁸, R³⁰, R³², R³⁴, R³⁶, R³⁸, R³⁹, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁷ and R⁴⁸ are, independently, C₁₋₆ alkyl (optionally substituted by halo, hydroxy, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₆ cycloalkyl, C₅₋₆ cycloalkenyl, S(C₁₋₄ alkyl), S(O)(C₁₋₄ alkyl), S(O)₂(C₁₋₄ alkyl), heteroaryl, phenyl, heteroaryloxy or phenyloxy), C₃₋₇ cycloalkyl, phenyl or heteroaryl; wherein any of the immediately foregoing phenyl and heteroaryl moieties are optionally substituted with halo, hydroxy, nitro, S(C₁₋₄ alkyl), S(O)(C₁₋₄ alkyl), S(O)₂(C₁₋₄ alkyl), S(O)₂NH₂, S(O)₂NH(C₁₋₄ alkyl), S(O)₂N(C₁₋₄ alkyl)₂, cyano, C₁₋₄ alkyl, C₁₋₄ alkoxy, C(O)NH₂, C(O)NH(C₁₋₄ alkyl), C(O)N(C₁₋₄ alkyl)₂, CO₂H, CO₂(C₁₋₄ alkyl), NHC(O)(C₁₋₄ alkyl), NHS(O)₂(C₁₋₄ alkyl), C(O)(C₁₋₄ alkyl), CF₃ or OCF₃;

R^{21} , R^{23} , R^{25} , R^{28} , R^{30} , R^{34} , R^{35} , R^{36} , R^{41} , R^{42} , R^{43} , R^{44} , R^{45} , R^{46} and R^{47} may additionally be hydrogen; or a pharmaceutically acceptable salt thereof or a solvate thereof.

- 5 2. Process for preparing of the compounds as claimed in claim 1.
3. A pharmaceutical composition which comprises a compound as claimed in claim 1, or a pharmaceutically acceptable salt thereof or solvate thereof, and a pharmaceutically acceptable adjuvant, diluent or carrier.
- 10 4. A compound as claimed in claim 1, or a pharmaceutically acceptable salt thereof or solvate thereof, for use as a medicament.
- 15 5. A compound as claimed in claim 1, or a pharmaceutically acceptable salt thereof or solvate thereof, in the manufacture of a medicament for use in therapy.
- 20 6. A method of treating a CCR5 mediated disease state comprising administering to a patient in need of such treatment an effective amount of a compound as claimed in claim 1, or a pharmaceutically acceptable salt thereof or solvate thereof.

